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ScienceDirect

Neuromuscular Disorders 24 (2014) 40–42

www.elsevier.com/locate/nmd

Case report

Myasthenia gravis and thymoma coexisting with myotonic dystrophy type 1 ☆

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Received 17 January 2013; received in revised form 20 July 2013; accepted 2 September 2013

Abstract

We describe a 34-year old man presenting with subacute generalized myasthenic symptoms. His clinical features and laboratory investigations demonstrated both myasthenia gravis and myotonic dystrophy type 1. The computerized tomography of chest revealed anterior mediastinal mass. The lymphocyte-rich thymoma was removed surgically and he received radiotherapy. Recent observations suggested that the patients with myotonic dystrophy may have an increased risk of benign and malignant tumours but its coexistence with thymoma is very rare. The risk of thymoma associated with myotonic dystrophy is unknown.

Keywords: Myotonic dystrophy; Thymoma; Neoplasm

1. Introduction

Myotonic dystrophy is an inherited disease characterized by weakness, myotonia and early onset cataracts. It is a slowly progressive multisystemic disorder that affects the heart, eyes and, gastrointestinal, endocrine and central nervous systems [1]. Myotonic dystrophy is the most common form of muscular dystrophy in adults with prevalence of 1 case per 8000 people [2].

Molecular genetic studies have identified two types of myotonic dystrophy. Type 1 (DM1) is caused by a CTG repeat expansion in the untranslated region of the dystrophia myotonica protein kinase (DMPK) gene on chromosome 19q13.3, and type 2 (DM2) results from a CCTG repeat expansion in intron 1 of the zinc finger 9 gene on chromosome 3q21. The proportions of myotonic dystrophy patients with DM1 and DM2 are unknown [1].

Recent studies have suggested that myotonic dystrophy is associated with an increased risk of benign and malignant tumours [2–5]. The association of myotonic dystrophy with thymoma and myasthenia gravis is very rare [2,3,6]. In this report, we present a patient with myotonic dystophy coexisting with myasthenia gravis and thymoma.

2. Case

A 34-year-old man was admitted to the hospital with a 2 weeks history of fatigue, dysphagia, eyelid fall and weakness. His initial complaints were fatigue and ptosis of the left eyelid. Difficulty swallowing and, weakness that fluctuated throughout the day in his arms, legs and neck muscles occurred within 2 weeks. His medical history, revealed infertility with oligospermia. His older brother had been surgically treated for early onset cataract and was also infertile with oligospermia.

A neurological examination, demonstrated mild ptosis in his left eyelid and bilateral facial weakness, but no

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0960-8966
http://dx.doi.org/10.1016/j.nmd.2013.09.001

Fig. 1. Ptosis and facial weakness.

oculomotor paresis was observed. (Fig. 1) There was generalized weakness in his arms, legs and neck muscles. He had nasal speech and complained of difficulty swallowing and chewing. The Simpson test was positive. These findings suggested a diagnosis of myasthenia gravis, but we also observed handgrip myotonia during a thorough examination in the neuromuscular clinic. He had percussion myotonia of the thenar and tongue muscles. (Fig. 2) He had been unaware of his myotonic symptoms.

His complete blood count, erythrocyte sedimentation rate, serum chemistries and thyroid hormone levels were normal. Anti-thyroperoxidase and anti-thyroglobulin antibodies were negative. The acetylcholine receptor (AChR) antibody titre was 14 nmol/L (normal <0.5 nmol/L). Needle electromyography demonstrated myotonic discharges, short-duration motor unit action potentials and early recruitment. There was a 20% decremental response to 3–5 Hz repetitive stimulation. A computerized tomography scan of his chest showed a 2.3 × 1.8 cm anterior mediastinal mass. Echocardiography showed diastolic dysfunction of the left ventricle.

Fig. 2. Myotonia with percussion of the tongue.

His brother was invited to undergo a neurological examination; he had bilateral weakness of the facial and neck flexor muscles and, eyelids and grip myotonia. Percussion myotonia of the thenar and tongue muscles was also noted. He was also unaware of his myotonic symptoms. Needle EMG revealed myotonic discharges, short duration motor unit action potentials, early recruitment. Repetitive nerve stimulation test at 3–5 Hz was normal.

The clinical features, acetylcholine receptor antibody positivity and decremental response to repetitive stimulation confirmed the diagnosis of myasthenia gravis. However the presence of clinical, electrophysiological myotonia and positive family history supported a diagnosis of myotonic dystrophy. A molecular genetic analysis revealed an expansion due to 80 CTG repeats in the untranslated region of DMPK gene. He was diagnosed with both myasthenia gravis and myotonic dystrophy type 1 based on his clinical and laboratory features.

The patient was started on pyridostigmine at a dosage 60 mg three times daily and administered intravenous immunoglobulin (IVIG) (total dose 2 gr/kg for 3 days) for his bulbar symptoms. After IVIG therapy, his dysphagia, ptosis, and extremity and neck weakness improved, but his nasal speech and facial weakness continued. Oral prednisolone (60 mg/day) was added to the treatment regimen and he underwent surgery for the anterior mediastinal mass. The mass was found to be a type 1B thymoma (lymphocyte-rich thymoma) and the mediastinal fat tissue was infiltrated. He subsequently received radiotherapy.

At a 10-months follow up, his myasthenic symptoms were improved. However, his myotonic symptoms and facial weakness remained the same without troubling him. Electrodiagnostic tests and AChR antibody titre were repeated after 10 months. Needle EMG study demonstrated myotonic discharges and short duration motor unit potetntials and early recruitment. There was no decremental response to 3–5 Hz stimulation. AChR antibody titre did not decrease (15 nmol/L).

3. Discussion

Myotonic dystrophy is very rarely associated with both thymoma and myasthenia gravis, and only nine cases with myotonic dystrophy and thymoma have been reported since 1969 [2,6–12]. Only two cases had both thymoma and myasthenia gravis. Additionally, three cases with myotonic dystrophy and myasthenia gravis have been reported [13–15].

Recent studies have suggested that patients with myotonic dystrophy have an increased risk of benign and malignant tumours [2–5]. Pilomatricoma is the most commonly reported tumour and several reports have suggested that multiple basal cell carcinomas may be a phenotypic variant of myotonic dystrophy [2]. Gadalla et

al. reported an increased risk for malignancy of the endometrium, brain, ovary and colon [3]. Win et al. also demonstrated an increased risk of thyroid cancer and choroidal melanoma compared with the general population. However their study also indicated an increased risk for cancers of the prostate and testicles [4]. In Das' study, myotonic dystrophy type 1 and female gender were associated with tumour development. They suggested that patients who were female or had myotonic dystrophy type 1 were more likely to develop tumours than male or individuals with type 2 [5].

Several mechanisms for the increased cancer risk have been postulated, including; RNA-mediated alterations in tumour suppressor genes, oncogene expression and modification of the coding features of proteins [3]. The CTG expansions in DMPK and the CCTG expansions in ZNF9 do not alter the protein coding-portion of their respective genes, but their mutant mRNA are sequestered in the nucleus and alter the function of RNA splicing factors such as muscleblind (MBNL1), and the CUG-BP1 and ETR-3-like factors (CELF) family of RNA binding proteins [1]. Mueller et al. hypothesized that tumour progression in myotonic dystrophy also involves the up regulation of beta catenin via the Wnt signaling pathway, possibly via the actions of RNA splicing factors (CUG-BP or MBNL). In human fibroblasts, CUG-BP1 has been shown to block calcireticulin mediated repression of p21 translation. Increased expression of p21 is a somatic molecular characteristic of thymomas. p21 plays a major role in oncogenesis and has also been implicated in apoptosis, terminal differentiation and replicate senescence via interaction with such well known tumour suppressor genes as p53 and BRCA, as well as genes in the Wnt/beta catenin signaling pathway [1]. DMPK is a member of a large gene family that contains cancer susceptibility genes such as RET (multiple endocrine neoplasia type 2), STK11 (Peutz-Jeghers syndrome) and, ALK (neuroblastoma) [5]. DMPK may also be a cancer susceptibility gene.

In this case, there is an association between myotonic dystrophy and thymoma. Myasthenic symptoms are due to paraneoplastic myasthenia gravis.

The risk of thymoma in patients with myotonic dystrophy is unknown. The concurrent presence of thymoma and myotonic dystrophy has been reported in only a few case reports. If the symptoms of myotonic dystrophy in a patient coexist with thymoma and myasthenia gravis are subtle or mild, the diagnosis may be missed. It is important to be aware of these associations because early diagnosis with proper treatment will provide a better outcome.

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